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Medically assisted reproduction and birth outcomes: a within-family analysis using Finnish Population Registers

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Abstract

Background Children born after medically assisted reproduction (MAR) are at higher risk of adverse birth outcomes than naturally conceived children. It is not known to what extent the excess risk should be attributed to harmful effects of the treatment or to pre-existing parental characteristics that confound the association.

Methods We analysed birth weight, gestational age, risk of low birth weight, and risk of preterm birth among MAR- and naturally conceived children using Finnish population registers covering 65,723 children born in 1995-2000. First, we estimated the differences in birth outcomes by mode of conception in the general population using standard multivariate methods that controlled for observed factors (e.g., multiple birth, birth order, and parental socio-demographic characteristics). Second, we used a sibling-comparison approach that has not been used before in MAR research. We compared MAR-conceived children to their naturally conceived siblings, and thus controlled for all observed and unobserved factors shared by siblings. The latter analysis included 1245 children.

Findings MAR-conceived children had worse outcomes than naturally conceived children for all outcomes, even after adjustments for observed child and parental characteristics (e.g., 60gr [95% CI: -34 to -86] lower birth weight; 2.15-percentage point [95% CI: 1·07 to 3·24] increased risk of preterm delivery). In the sibling comparison, the gap in birth outcomes was attenuated, such that the relationship between MAR and adverse birth outcomes was statistically and substantively weak for all outcomes (e.g., 31gr [95% CI: -22 to 85] lower birth weight; 1.6 percentage points [95% CI: -1·3% to 4·4%] increased risk of preterm delivery).

Interpretation MAR-conceived children face an elevated risk of adverse birth outcomes. However, our results indicate that this increased risk is largely attributable to factors other than the MAR treatment itself.

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Research in context

Evidence before this study

We searched for studies analysing the association between Medically Assisted Reproduction and birth outcomes within families who had at least one child conceived through MAR and one child conceived naturally, published in any language up until March 2018 (with no specified earliest date). We searched in PubMed and Google Scholar using relevant terms ("Medically Assisted Reproduction", "Assisted Reproductive Technology", "birth outcomes", "low birth weight", "preterm", "siblings", "within family"). We found only three studies that compared MAR- and naturally conceived children from the same families. These studies, which reported mixed findings, suffered from two major limitations. First, they relied on random-effects models, which are biased when unobserved random effects (e.g., measuring health) are correlated with observed covariates (e.g., maternal age, socioeconomic status). Second, they focused on children conceived through IVF only, and included children born after other fertility treatments (ovulation induction or artificial insemination) in the naturally conceived group. This approach may have biased the estimated MAR effects towards zero, as children conceived through other MAR treatments have worse birth outcomes than naturally conceived children.

Added value of this study

The current study considered all MAR-conceived children, and adopted a sibling-comparison model with a fixed-effects specification that is more appropriate (than random-effects models) for determining whether the MAR treatment had an independent effect on birth outcomes, as it fully controlled for unobserved parental characteristics shared by siblings. Moreover, it relied on a uniquely high-quality register dataset that was large enough to facilitate sibling comparisons, free of loss to follow-up and self-report biases.

Implications of all the available evidence

As a group, children born after MAR are, in absolute terms, at increased risk of adverse birth outcomes. But the results of the current study indicate that this elevated risk is likely attributable to factors other than the treatment itself. Understanding the risks associated with MAR treatment is very important for couples considering using MAR treatment to conceive, physicians advising patients about the risks of MAR, and public health policy-makers.

Introduction

Medically Assisted Reproduction (MAR) – i.e., reproduction brought about through treatments such as ovulation induction, artificial insemination, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with fresh/frozen embryo transfer – is one of the key achievements of reproductive medicine. The increasing number of children born after MAR, to date more than five million,[1] has motivated research about its impact on the well-being of children.

While previous studies have consistently found that children born after MAR have worse perinatal outcomes than children who were conceived naturally,[2-6] the mechanisms underlying this well-established association are not fully understood. First, worse outcomes could be related to the rates of multiple births, which are 10-20 times higher in the MAR subpopulation than in the general population, and are strong predictors of adverse birth outcomes.[7] Second, the association could be related to parental characteristics that predispose the parents to seek MAR treatments and to be at high risk of adverse birth outcomes, such as subfertility and advanced age, which are known risk factors for adverse birth outcomes.[4,8,9] However, the risk of adverse outcomes cannot be entirely attributed to multiple births, as singletons conceived through MAR are also at higher risk of adverse birth outcomes than singletons conceived naturally.[3,10] Existing studies have also found that although subfertility might play a role it cannot be considered as the only explanation for the poorer outcomes of the MAR subgroup relative to the overall population and that being born to an older mother is not associated with worse birth outcomes among children conceived through MAR.[4,11]

Consequently, the literature has suggested that some of the effects could be attributed to the MAR procedures themselves, [4,12,13] such as the freezing of embryos, the delayed fertilisation of the oocytes, and the hormonal treatments.[14] However, establishing an independent effect requires isolating the effects of the MAR procedures from the multiple factors that might confound the association – many unobserved by the researcher. The majority of existing studies have analysed the association between MAR and birth outcomes by comparing MAR- and naturally conceived children in different families, and by adjusting for a limited set of observed characteristics.[3,4] The results of such studies may suffer from bias due to residual confounding. For example, the health of the mother, which may influence the likelihood of adverse birth outcomes, is unlikely to be fully captured by observed control variables.

This study is the first to analyse the potentially harmful effects of MAR treatment using a sibling-comparison approach, which enables us to account for all observed and unobserved parental characteristics shared by siblings.[15] We used large-scale Finnish register data to analyse the association between MAR and birth outcomes within families in which at least one child was born after MAR and one child was conceived naturally. Three earlier MAR studies compared siblings, but these studies suffered from two major limitations. First, they relied on random-effects models, which are biased when unobserved random effects (e.g., measuring health) are correlated with observed covariates (e.g., socioeconomic status).[16] Second, they focused on children conceived through IVF only, and assigned children born after other fertility

treatments to the naturally conceived group.[17-19] We consider all MAR-conceived children; adopt a sibling-comparison model with a fixed-effects specification that is best suited for establishing whether the MAR treatment has an independent effect on birth outcomes; and rely on a uniquely high-quality register dataset that is large enough to facilitate sibling comparisons, without loss to follow-up and self-report bias.

Methods

Study population

We used data from Finnish administrative registers covering a 20% random sample of households with at least one child aged 0–14 at the end of 2000. The linkages between different registers were carried out by Statistics Finland using personal identification numbers. We included birth cohorts 1995–2000 because the information on whether the child was conceived through MAR or naturally was available from 1995 onwards.

Birth outcomes

Information on four birth outcomes was extracted from the Finnish Medical Birth Register (MBR): birth weight (in grams), gestational age at birth (in days), and indicators for low birth weight (LBW, less than 2500g at birth), and whether the child was preterm (less than 37 weeks of gestation).

Medically Assisted Reproduction (MAR)

We identified children who were conceived through MAR from purchases of prescription medication using the method developed by Hemminki et al., which has been found to be reliable.[20] There are four main MAR techniques (ovulation induction, artificial insemination, IVF and ICSI with fresh/frozen embryo transfers) with an associated common pattern of fertility drugs. We retrieved from the National Prescription Register information on all prescription medication purchases from Finnish retail pharmacies, regardless of whether the medication was prescribed in the public or private sector. The Prescription Register provides information on the day of purchase, the name and class of the drug, and the size and quantity of packages. By combining each woman's purchases of fertility drugs with her child's date of birth (retrieved from the MBR), we were able to identify children conceived through MAR.

Control variables

We considered a range of child and parental characteristics that are associated with both conceiving through MAR and with the risk of adverse birth outcomes. The child characteristics retrieved from the MBR were sex, multiple birth, and birth order (1, 2, 3, or higher of live births).

The mother's characteristics included mother's age at birth (continuous), whether the mother smoked during pregnancy (binary), deciles of household income, highest level of education in the household (tertiary or below), and the marital status of the parents. Because the aim of the study was to isolate the effects of MAR from these of confounders, the models did not include

adjustments for mediators – e.g, gestational age or gestational hypertension – that could be on the causal pathway between MAR and birth outcomes.

Statistical analyses

We evaluated the association between MAR and birth outcomes using two approaches. The standard approach used in the literature consists of analysing the association between MAR and birth outcomes by comparing children born in different families. In order to account for confounders, these models included controls for observed child and parental characteristics. We refer to these models as *between-family* comparisons.

The alternative approach was based on comparing siblings born to the same parents, but conceived either naturally or through MAR; we refer to these models as *within-family* comparisons. Also known as sibling fixed effects, the *within-family* model includes an indicator for each sibling group, and identifies the association between MAR and birth outcomes from variation between siblings.[15] The main advantage of this model is that it fully accounts for unobserved family characteristics shared by siblings. These unobserved characteristics may, for example, include subfertility, which predisposes a couple to seek MAR treatment to conceive and to experience adverse birth outcomes. Observable characteristics that are not shared by siblings and vary over time, such as family income at the year of birth, were adjusted for as in standard regression analyses. We did not control for education and marital status of parents, which show little variation between siblings.

We estimated four regression models using Stata 14 for both the between- and within-family approaches. We estimated linear models on the continuous outcomes (birth weight and gestational age) and linear probability models on the binary outcomes (LBW and preterm birth), in which the model coefficients were interpretable as marginal effects.[15] The baseline model documented the descriptive association between MAR and each of the outcomes. Model 1 introduced controls for the child's sex and multiple birth, Model 2 introduced controls for birth order, and Model 3 introduced controls for parental characteristics.[4]

Children born after MAR are more likely to be first-born or of lower birth orders than their naturally conceived siblings.[8,17,21] Primiparity is associated with increased risk of adverse perinatal outcomes, and birth weight increases with increasing birth order[22]. Thus, birth order could partly explain the poorer birth outcomes of MAR-conceived children. To explore this possibility, we replicated the within-family analyses (baseline and Model 1) depending on whether the birth of the MAR-conceived child preceded (n=744) or followed (n=464) the birth of his/her naturally conceived sibling. For this last set of analyses, when the MAR-conceived child was born in-between two natural conceptions or when a naturally conceived child was born in between two MAR births, we only considered the first two births and excluded the third (or higher order) birth (n=33). We also excluded families (n=2) in which two consecutive MAR-conceived births were followed by a natural conception, or in which two natural conceptions were followed by a MAR-conceived birth.

Inclusion criteria and exclusions

We excluded cases of prescription medication purchases in the special refund category, which indicates the use of fertility drugs to treat other diagnosed medical conditions, such as cancer. We excluded births to mothers younger than age 20 (n=1,862) or older than age 45 (n=267) because it was unclear whether the women in these age groups were using the drugs for infertility or for other purposes. We dropped families with triplets (n=44). We kept in the analyses siblings who did not have the same father, as they were very small in number (n=4). Prevalence of missing data was negligible (the variable showing the highest level was smoking during pregnancy at 4%). The final sample included 65,723 children, 4% (n=2776) of whom were conceived through MAR. In 578 families, at least one child was conceived through MAR and one child was conceived naturally (n=1245).

Previous studies using sib-ship designs

Only three other studies have explored the association between MAR and birth outcomes using sib-ship designs. These studies relied on random-effects models. A key assumption for unbiased random-effects model is that the individual effects are uncorrelated with observed independent variables, an assumption that is often untenable.[16] To overcome this limitation, we use fixed-effects models, which do not require any assumption about the correlation between unobserved fixed effects and observed independent variables, and are thus more appropriate to fully control for unobserved parental characteristics shared by siblings.[16] Prior studies have also restricted the MAR category to IVF-conceived children only which could bias the MAR effects towards zero, as children conceived through other MAR treatments have worse birth outcomes than naturally conceived children.[21] To overcome this possible bias we included in the MAR group children who were conceived through IVF as well as other MAR techniques.

Results

Descriptive analyses

In the between-family analyses, MAR-conceived children had worse birth outcomes than the naturally conceived children (table 1). For example, the prevalence of LBW was 3·5% (n=2,203) in the naturally conceived group and 12·8% (n=355) in the MAR-conceived group. MAR-conceived children were also more likely than naturally conceived children to be the first-born (61·6% (n=1,710) vs. 37·7% (n=23,731)), and almost 10 times more likely to be a multiple birth (20·7% (n=575) vs. 2·1% (n=1,322)). Compared to mothers of naturally conceived children, mothers of MAR-conceived children were, on average, older, better educated, and less likely to smoke during pregnancy.

In the within-family comparisons, the differences in birth outcomes were reduced, but not eliminated. For example, 2·9% (n=18) of naturally conceived and 8·6% (n=54) of MAR-conceived children were LBW.

Regression results

The between-family results showed that MAR children had significantly worse birth outcomes than naturally conceived children: on average, they were lighter and born earlier, and were more likely to be LBW and to be born preterm (Table 2, coefficients for the control variables presented in Web Tables 1-4). For example, MAR-conceived children were, on average, 266gr lighter (95% CI: -296 to -235) and 9.8 percentage points (95% CI: 8·1 to 11·4) more likely to be preterm. The baseline associations were attenuated by around 60-70% when adjustments were made for sex and multiple births in Model 1; and by around 60-80% when a further adjustment was made for birth order in Model 2. However, in the fully adjusted Model 3, MAR-conceived children still had lower birth weight, increased risk of LBW, shorter gestation, and increased risk of preterm birth (e.g., on average 60gr (95% CI: -85 to -34) lighter and 2·1 percentage points more likely to be preterm (95% CI: 1·1 to 3·2) than naturally conceived children).

Our within-family comparison of MAR-conceived children with their naturally conceived siblings showed that the associations were weaker than in the between-family analyses. For example, in the baseline model, the difference in birth weight was 137g (95% CI: -189 to -85), and the difference in preterm delivery was four percentage points (95% CI: 1·4 to 6·7). In the fully adjusted Model 3, the difference in birth weight was only 31g (95% CI: -85 to 22), and the difference in preterm delivery was 1·6 percentage points (95% CI: -1·6 to 4·4). The patterns for gestational age and LBW were similar. In the fully adjusted within-family analysis, there was no evidence of a statistically significant association between MAR and birth any outcome (figures 1-4). These results were almost identical if we excluded multiple births from the analytical sample.

MAR children born before their naturally conceived siblings had lower birth weight and increased probabilities of LBW and preterm delivery (Table 3 and Figure 5). However, among MAR-conceived children born after their naturally conceived siblings, the association was reversed for birth weight, and was much smaller and not statistically significant for LBW and preterm delivery. Following adjustments for the child's sex and multiple births (Model 1), MAR-conceived children were 163 gr (95% CI: -220 to -105) lighter if they were born before their naturally conceived siblings, and 58gr (95% CI: -28 to 144) heavier if they were born after. Regardless of birth order, MAR-conceived children were, on average, born earlier than their naturally conceived siblings; but the risk of preterm birth was significantly higher only among MAR-conceived children born before their naturally conceived siblings.

Discussion

As a group, MAR-conceived children are at elevated risk of having low birth weight and being born preterm. This excess risk could be due to harmful effects of the treatment or to pre-existing parental characteristics that confound the association between MAR treatment and birth outcomes. Our analysis of birth outcomes in families with both MAR-conceived and naturally conceived children found only limited evidence that the excess risk could be attributed to the MAR treatment itself. When we compared MAR-conceived children to their naturally

conceived siblings, we found smaller and, after adjustments for multiple births and birth order, both statistically and substantively negligible associations between MAR and birth outcomes.

This study has several strengths. First, the dataset was large and allowed us to compare siblings conceived through MAR and naturally. Second, the data were not prone to self-selection or self-report bias because they were drawn from administrative registers and have a negligible level of missingness. Third, we relied on a methodological approach that enabled us to account for unobserved parental characteristics shared by siblings. Unlike prior studies, which compared MAR- and naturally conceived children in the same families using random-effects models, [17-19] we estimated fixed-effects models that fully control for unobserved parental characteristics shared by siblings, and are thus preferable when the aim is to isolate the effects of MAR from those of unobserved parental characteristics.[16] Moreover, we included in the MAR group children who were conceived with treatments other than IVF. In prior studies, these children were included in the reference category of naturally conceived children.

Our analysis has limitations that are important to note when considering the practical implications of the findings. First, although the use of the within-family approach minimized the confounding of unobserved parental characteristics in our estimates, it restricted our ability to generalize the results to all MAR-conceived children. A particular concern is that parents who have both MAR- and naturally conceived children are more likely to have used less invasive treatments, such as ovulation induction, that may not be as strongly associated with adverse birth outcomes, than more invasive treatments, such as IVF. Because we did not have access to the National Procedure Register, we could not reliably distinguish all IVF treatments from the less invasive treatments. A comparison with Hemminki et al.[20] indicated that in our data we underestimated the percentage of IVF-conceived children by about 10%. As a robustness check we estimated the models separately for the group of IVF-conceived children (40% of total MAR births), and the results support the main study argument. For the same reason, we could not distinguish fresh from frozen embryo transfers in IVF/ICSI cycles.[23] Whilst the fact that we could not analyze treatment types separately is a limitation, we believe that it is also justifiable to analyze MAR as a single category because there are a lot of common characteristics between couples who access different MAR treatments. For example, couples who seek any MAR treatment are unable to conceive naturally and suffer from sub-fertility, all treatment types involve some drug therapy, and undergoing any MAR treatment is a stressful process. Children who are conceived through any MAR treatment are more likely to be multiple birth and the first born. All these characteristics could negatively affect birth outcomes.

Second, we could not test whether the effects of MAR on birth outcomes vary according to the length of infertility, medication dose and number of treated cycles. Future work using larger samples and with longer follow-up should explore whether the effects of MAR on birth outcomes vary, for example, by the length of infertility. In addition, further analyses should evaluate whether the repercussions of MAR on child outcomes have changed over time (for example, single embryo transfer has become common practice resulting in a drop in multiple births)[2]. Finally, further within family fixed-effect analyses should aim to study the relationship

between MAR treatments and longer term health and social outcomes. Third, the within-family analyses have lowered the precision of the estimates because they reduced the sample size, which could in turn mean that the parameters were not statistically significant; the within-family confidence intervals overlapped with those of the between-family estimates. However, the within-family associations for all four outcomes showed parameter estimates that were both statistically and substantially negligible.

The fact that the within-family estimates are smaller than the between-family ones suggest that the association between MAR and adverse birth outcomes is confounded by unobserved factors related to both the probability of seeking MAR treatment to conceive and the probability of adverse birth outcomes. These unobserved factors could be parental underlying health, subfertility, psychological stress and genetic factors. Three other studies have looked at families with at least one MAR- and one naturally conceived child. Our results are not fully comparable to those of previous studies because we used fixed- (instead of random-) effects models, and we assigned children conceived with treatments other than IVF to the MAR (rather than the reference) category. Moreover, unlike in previous studies, we did not control for mediators like gestational age when analysing the association between MAR and birth weight/LBW. However, despite these differences, our study and these three other studies all suggest that any MAR-specific effect on birth outcomes (though statistically significant in two studies [18,19]) is small, and is unlikely to be clinically relevant.

The results also point to the importance of considering factors that vary across families and between siblings. In particular, MAR-conceived children are more likely than naturally conceived children to be the first-born child. Being the first-born is a known risk factor for adverse birth outcomes, and our results show that the effect of birth order is stronger than the effect of MAR in both the between- and within-family analyses. For example, the analyses for birth weight show that the effect of being the first-born rather than the second- or third-born was, respectively, three and four times higher than the effect of MAR (Web Table 1). Moreover, in the within-family analyses, the association between MAR and birth outcomes changed substantially based on whether the MAR child was born before or after his/her naturally conceived sibling. These findings support the argument that the treatments per se have little or no effect on the risk of adverse birth outcomes, and that any effects that exist are considerably smaller than the effect of being the first-born. Yet the impact on birth outcomes of birth order has been much less discussed in the literature than the negative impact of MAR.

The question of whether seeking MAR treatment to conceive increases the risk of adverse pregnancy outcomes is important given that the utilization of these techniques has been increasing strongly in virtually all advanced societies since the 1980s.[1,24] Understanding these risks is essential for couples considering using MAR treatments to conceive, physicians advising patients about the risks of MAR, and public health authorities. Our results indicate that children born after MAR are, in absolute terms, at elevated risk of adverse birth outcomes; but that this higher risk is likely attributable to factors other than the treatment itself.

Conflicts of interest statement
None to declare

Role of Founding Source
The study sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Author's contribution
AG conceived the idea. AG, HR, and MM designed the study. HR wrote the software program to identity MAR treatments from prescription data (following earlier work by RK), with the support of RK and AG. AG and HR analysed the data. All authors contributed to the interpretation of the results. AG and MM wrote the first draft of the paper. All authors reviewed and edited subsequent drafts. All authors read and approved the final manuscript.

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Table 1 Birth outcomes and characteristics of women giving birth in Finland in 1995-2000, by mode of conception

	Overall population			Within-family sample		
	NC (n=62,947)	**MAR (n=2,776)**	**P value**	**NC (n=620)**	**MAR (n=625)**	**P value**
Birth outcomes						
Birth weight in grams, mean (sd)	3551 (556)	3286 (694)	p<0.0001	3594 (547)	3428 (665)	p<0.0001
Low birth weight (%)	3.5	12.8	p<0.0001	2.9	8.6	p<0.0001
Gestational age in days , mean (sd)	278 (12)	271 (17)	p<0.0001	278 (11)	275 (15)	p<0.0001
Preterm (%)	4.9	14.6	p<0.0001	4.8	9.4	0.002
Covariates						
First-order birth (%)	37.7	61.6	p<0.0001	26.6	47.5	p<0.0001
Maternal age at birth, mean (sd)	29.6 (5)	32.0 (5)	p<0.0001	31.0 (5)	31.0 (4)	0.671
Household income decile, mean (sd)	5.3 (3)	6.3 (3)	p<0.0001	5.9 (3)	6.2 (3)	0.04
Household with tertiary education (%)	53.0	65.3	p<0.0001	66.8	68.5	0.593
Parents married the year of the child's birth (%)	66.4	79.4	p<0.0001	82.9	81.6	0.619
Mother smoked during pregnancy (%)	14.4	6.2	p<0.0001	4.2	5.8	0.253
Multiple birth (%)	2.1	20.7	p<0.0001	1.0	10.9	p<0.0001
Child sex: girl (%)	49.1	48.6	0.725	46.3	45.4	0.769
Number of observations	65723			1245		

Note: NC=naturally conceived; MAR=conceived with the help of Medically Assisted Reproduction methods. P values obtained through Chi Square test (for all categorical variables) and t test (for all continuous variables).

Table 2 MAR coefficients obtained by estimating between- (n=65,723) and within-family (n=1,245) linear models on the birth outcomes of women giving birth in Finland 1995-2000 (reference category: naturally conceived children)

		Baseline	P Value	95% CI	Model 1 = child sex + multiple birth	P Value	95% CI	Model 2=Model 1+ child birth order	P Value	95% CI	Model 3=Model 2+ family characteristics[a]	P Value	95% CI
Between family	**Birth weight (gr)**	-266	p<0.0001	-296 - -235	-98	p<0.0001	-124 - -72	-47	p<0.0001	-73 - -22	-60	p<0.0001	-86 - -34
	Gestational age (days)	-6	p<0.0001	-7 - -5	-2	p<0.0001	-3 - -2	-2	p<0.0001	-3 - -1	-2	p<0.0001	-3 - -1
	LBW (percentage points)	9.35	p<0.0001	7.88 - 10.81	2.24	p<0.0001	1.31 - 3.17	1.43	0.003	0.49 - 2.36	1.61	0.001	0.68 - 2.55
	Preterm (percentage points)	9.75	p<0.0001	8.10 - 11.41	2.78	p<0.0001	1.71 - 3.86	2.01	p<0.0001	0.93 - 3.10	2.15	p<0.0001	1.07 - 3.24
Within family (sibling fixed effects)	**Birth weight (gr)**	-137	p<0.0001	-189 - -85	-82	0.001	-132 - -32	-34	0.209	-88 - 19	-31	0.252	-85 - 22
	Gestational age (days)	-2	p<0.0001	-4 - -1	-1	0.07	-2 – 0	-1	0.056	-3 - 0	-1	0.059	-3 - 0
	LBW (percentage points)	4.66	p<0.0001	2.39 - 6.93	2.31	0.019	0.38 - 4.25	1.57	0.138	-0.51 - 3.65	1.42	0.18	-0.66 - 3.51
	Preterm (percentage points)	4.04	0.003	1.36 - 6.73	2.03	0.107	-0.44 - 4.49	1.54	0.277	-1.24 - 4.31	1.56	0.278	-1.26 - 4.38

Note: [a] Model 2 includes control for: birth order, maternal age at birth, smoking during pregnancy, household income decile. The between family model also includes adjustment for parents' marital status and for whether at least one of the two parents holds a tertiary education degree. Reference category: naturally conceived children

Table 3 Within-family MAR coefficients obtained by estimating linear models on the birth outcomes among women giving birth in Finland 1995-2000, by birth order of MAR vs. NC conceptions

		Baseline	P value	Model 1 = child sex + multiple birth	P value
MAR followed by NC (n=744)	**Birth weight (gr)**	-224	p<0.0001	-163	p<0.0001
	Gestational age (days)	-2	0.036	0	0.792
	LBW	5.49	p<0.0001	2.72	0.029
	Preterm	4.93	0.007	2.11	0.195
NC followed by MAR (n=464)	**Birth weight (gr)**	8	0.845	58	0.183
	Gestational age (days)	-4	0.001	-2	0.019
	LBW	3.36	0.061	1.36	0.398
	Preterm	2.31	0.29	1.30	0.522

Note: NC=naturally conceived; MAR=conceived through the help of Medically Assisted Reproduction. Reference category: naturally conceived children

Figure 1 Mean birth weight for MAR children (reference: naturally conceived) from estimating between- and within-family models for women giving birth in Finland 1995-2000 (Table 2), with 95% confidence intervals

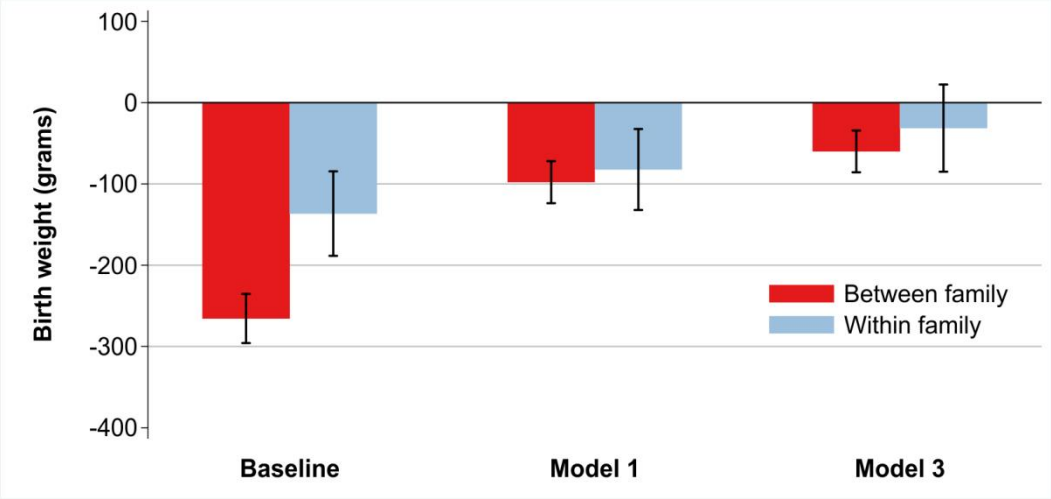

Figure 2 Mean gestational age for MAR children (reference: naturally conceived) from between- and within-family models for women giving birth in Finland 1995-2000 (Table 2), with 95% confidence intervals

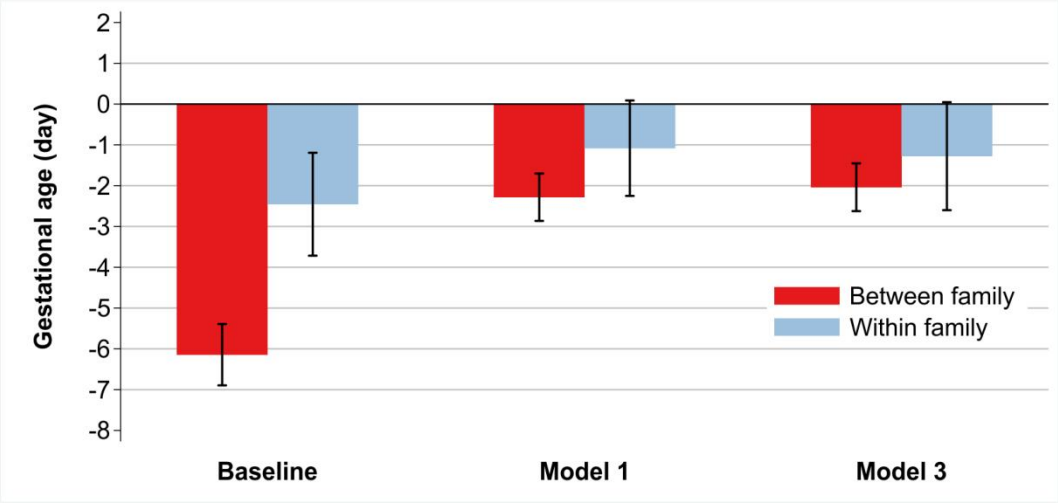

Figure 3 Percentage change in the probability of LBW for MAR children (reference: naturally conceived) from between- and within-family models for women giving birth in Finland 1995-2000 (Table 2), with 95% confidence intervals

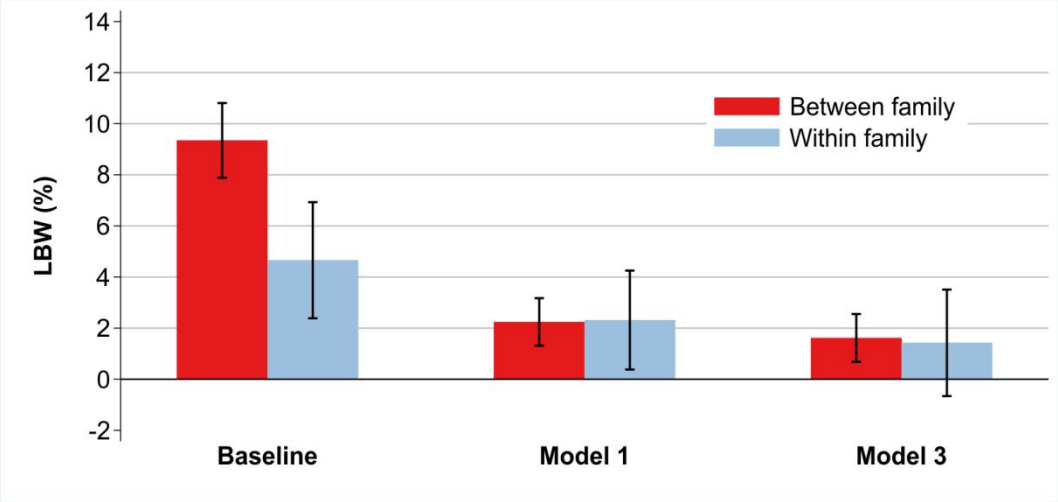

Figure 4 Percentage change in the probability of preterm birth for MAR (reference: naturally conceived) children from between- and within-family models for women giving birth in Finland 1995-2000 (Table 2), with 95% confidence intervals

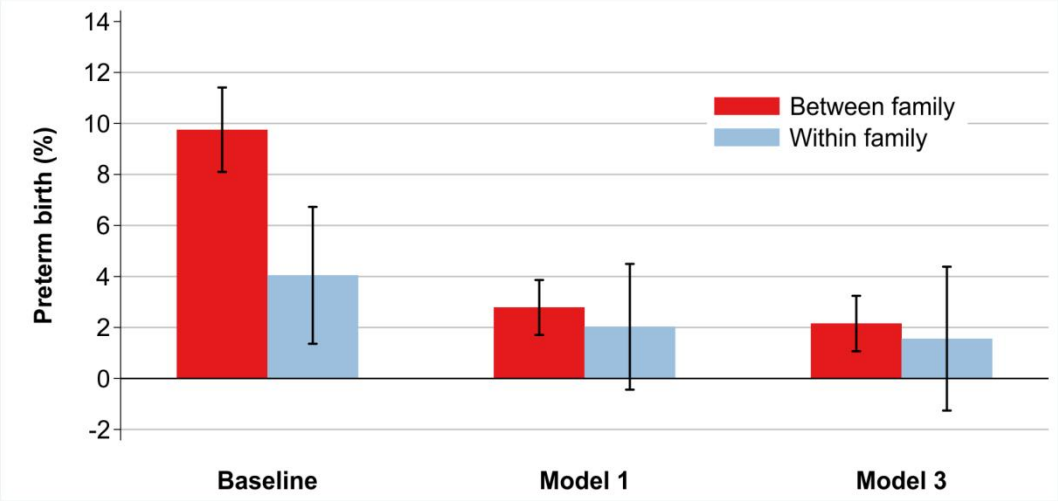

Figure 5 Mean birth weight for MAR children from within-family models, by birth order of MAR and naturally conceived siblings for women giving birth in Finland 1995-2000 (Table 3), with 95% confidence intervals